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Brain Substrates of Infant–Mother Attachment: Contributions of Opioids, Oxytocin, and Norepinephrine

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NELSON, E. E., PANKSEPP, J. *Brain substrates of infant–mother attachment: contributions of opioids, oxytocin, and norepinephrine*. NEUROSCI BIOBEHAV REV **22**(3) 437–452, 1998.—The aim of this paper is to review recent work concerning the psychobiological substrates of social bonding, focusing on the literature attributed to opioids, oxytocin and norepinephrine in rats. Existing evidence and thinking about the biological foundations of attachment in young mammalian species and the neurobiology of several other affiliative behaviors including maternal behavior, sexual behavior and social memory is reviewed. We postulate the existence of social motivation circuitry which is common to all mammals and consistent across development. Oxytocin, vasopressin, endogenous opioids and catecholamines appear to participate in a wide variety of affiliative behaviors and are likely to be important components in this circuitry. It is proposed that these same neurochemical and neuroanatomical patterns will emerge as key substrates in the neurobiology of infant attachments to their caregivers. © 1998 Elsevier Science Ltd. All rights reserved.

INTRODUCTION

MAMMALIAN INFANTS display affiliative behaviors and form 'attachment bonds' with their caregivers. These bonds are characterized by selective approach and interaction with specific individuals, and display of affective distress during acute periods of separation from these individuals. It has been theorized that social attachment serves to maintain close physical proximity and elicit care from a primary caregiver, which in turn increases the probability of the young surviving to maturity and reproducing (27).

Although the evolutionary advantages of attachment have been discussed for some time, only recently have specific mechanistic hypotheses been advanced concerning the underlying neural substrates of these behaviors (174). The research precedents for the existence of attachment systems in the brain were established by the well-known behavioral research programs of Harry Harlow (72–74) and John Paul Scott (181,181), which will not be detailed here.

We believe that the neural mechanisms which underlie attachment are organized into a socially directed motivational system within the brain (151,174). This neural system emerges in infancy and continues to modulate affiliative behaviors throughout the life-span. Although the level of social activity varies greatly in adults of different species (50), all mammals engage in some degree of affiliative behavior after weaning. Such behaviors range from rough and tumble play (57,161), to sexual and parental behaviors (107,111), to maintenance of group cohesiveness (5). Several anatomical and neurochemical similarities have been found in these varied affiliative behaviors across species, which suggest the existence of a common neural system. We believe the ontogenetic roots of this affiliative system may be found in infant social attachment.

The focus of this paper will be on the mechanistic nature of attachment processes in the brains of infant animals. We will attempt to integrate the literature on rat pup attachment with data on the neural substrates of adult affiliative behavior, and will assert that infant–mother attachment shares many neural substrates with affiliative and attachment behaviors expressed in adults. Cross-species and cross-situational generality have been identified for oxytocin, endogenous opioids, and norepinephrine. This is not meant to be a comprehensive review of the literature on the neural substrates of affiliative behavior. Our purpose is merely to suggest that sufficient evidence exists to include these three neurochemical systems as a part of a neural circuit which regulates affiliative and attachment behaviors across mammalian species and across development.

One critical conceptual question which we hope will emerge from the present discussion is whether there is a single or multiple evolutionary antecedents for attachment. If there is no single source process, but rather, the converging influences of multiple processes (Fig. 1), such as the contributory effects of contact comfort, energy and thermoregulatory effects, as well as other forms of

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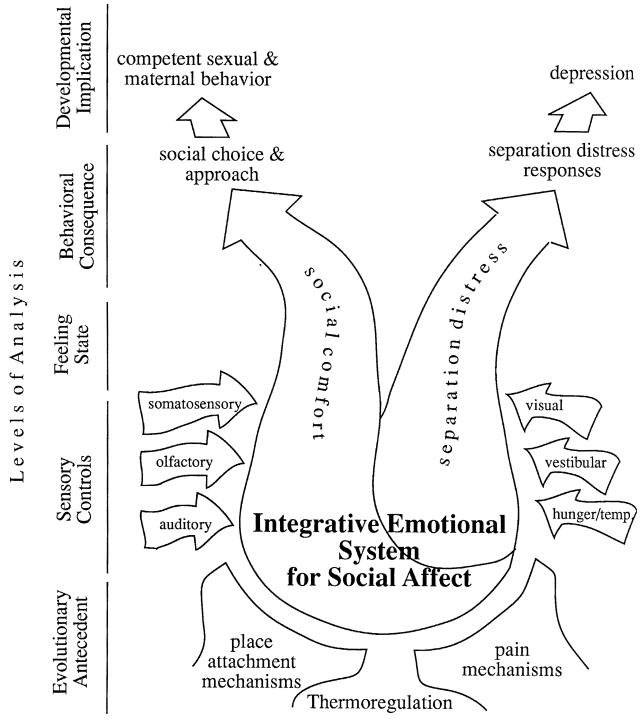

FIG. 1. Schematic depiction of the neurobiological foundations, inputs, and consequences of attachment and affiliative behavior in mammals. Figure reprinted with permission of the New York Academy of Sciences.

emotional-distress alleviation and modulation, then we will undoubtedly have to deal with patterns of complexity that will vary substantially from species to species. Indeed, it has been argued that in primates attachments to peers and to parents reflect the existence of independent motivational systems (117), but this may not contradict the possibility that distinct mechanisms share many underlying controls, such as common neurochemistries. Thus, we believe that in spite of a diversity of modulatory controls, there are reasons to believe that important general principles (i.e. neural systems) exist which underlie the integrative aspects of attachment in all mammalian species.

We believe that a core-integrative attachment system exists within the mammalian brain upon which the various inputs converge. This putative attachment system is organized bi-dimensionally, and consists of at least two major affective components, one devoted to the perceptions of social-absence and one devoted to the pursuit of social-engagement (153,159). We believe that this is organized bi-dimensionally rather than along a single axis because the neural circuits for social engagement (maternal behavior, and rough and tumble play for example), appear to be quite different from those that inhibit the expression of separation distress (77,132,144).

Although the neurobiological nature of this attachment system is not well understood, we will entertain the idea that this mechanism is an evolutionary-derived outgrowth of mechanisms which originally subserved basic needs such as energy balance, thermoregulation, place-attachments, and pain perception. Presumably, the preexisting energy balance, thermoregulatory and place-attachment mechanisms contributed more to the evolving brain mechanisms which monitor social presence, while the pain mechanisms made stronger contributions to sub-components which aroused emotional distress during social-absence.

At present, no direct data exist on the nature of place-attachment mechanisms in the brain, even though the vast literature on place-preference conditioning in animals could be used to generate credible hypotheses (178). For instance, place-preference is easily established by pairing specific environments with opiate administration, and brain opioids contribute significantly to the modulation of social attachments.

The rat model of social attachment

We focus here on the rat because of the diversity of psychobiological work that has been conducted on the social behavior of both young and adult rats. However, it must be emphasized that infant rats have some characteristics which make them less than an ideal species for study, such as a remarkably weak separation response (160). Perhaps for this reason, the study of juvenile rats has provided a remarkably effective model for analyzing social engagement, such as rough-and-tumble play (144,161). Unlike many other species, in rats prior social isolation strongly promotes play, presumably because the animals do not experience separation distress intensely during juvenile life (148). Thus, while rat models may have certain disadvantages for studying the mechanisms of separation distress, they may represent an excellent model for the study of the prosocial arm of the attachment system (see Fig. 1).

As infants, rats display motivation to seek out maternal contact and care (81,110), and rats of many ages show evidence of specific social learning and individual recognition (67,110). In addition rat pups display some reaction to separation such as behavioral activation and agitation during acute periods of maternal separation (78,94,130, 187), and rat pups exhibit some transient symptoms that resemble the anaclitic depression syndrome which has been described in isolated human infants after prolonged periods of separation (79,196), however these are not related to the absence of a specific individual.

Thus, some important affiliative behaviors are present in the preweanling rat, but at least part of their affiliative system, namely the one that responds uniquely to the perception of social isolation, appears to be comparatively weak relative to many other species. Still, the convenience of the rat model and the extensive literature that exists on their many other affiliative behaviors, such as play, sexual and maternal behaviors, continues to promote psychobiological research on the prosocial brain-mechanisms of rats. There is reason to believe that many general principles of the mammalian attachment system are conserved in infant rats' affiliative tendencies, and the unique adaptations of rats can help alert us to critical conceptual issues that may need to be kept in mind when discussing bonding mechanisms across species. If carefully considered, both the peculiarities and particulars of the rat may provide special insights into the nature of the underlying attachment mechanisms, as well as clues about the evolutionary history of such mechanisms.

Affiliative behavior of the infant rat

Prior to weaning, rats spend the majority of their time

huddled in a group with littermates and the dam to form a dynamic and cohesive social unit. If removed from this social group for a relatively short period of time rats undergo a period of behavioral activation which is characterized by an increase in activity (187), increases in heart and respiration rate (78), corticosterone release (198) and the production of ultrasonic vocalizations (130). A similar behavioral profile is seen in many mammalian infants subjected to social isolation (72,73,181,182), and we believe represents the expression of a generalized pattern of separation distress. Prolonged or repeated bouts of social isolation in infant rats will result in retardation of growth related enzymes (108), declines in heart rate (79), a heightened responsiveness of the hypothalamic–adrenal stress response system (175), and generalized behavioral retardation (79) characteristic of a depression like state.

Many of the preweanling pups' affiliative behaviors appear to be mediated by thermo-tactile sensory domains. For example, very young rats will spend as much time huddling with a warm fur-covered tube as with a conspecific, although a preference for the conspecific does emerge during the second post-natal week (3). Furthermore, isolation-induced ultrasonic vocalizations can be virtually eliminated if rats are placed in a warm chamber (25), and greatly attenuated if isolated in the presence of various thermal and tactile stimuli which approximate the mother or littermates (79). Furthermore, the retardation in growth hormones, and hyper-responsivity of the adrenocortical system that is seen in socially deprived rats can be reversed if isolated rats are stroked with a paintbrush or allowed tactile contact with a conspecific (108,198).

The importance of thermal and tactile sensory input to the expression of social behavior generalizes beyond the preweanling period. Tactile interaction appears to be of primary importance for rough and tumble play in juvenile rats (191,192) and also plays an important role in the social behavior of adult rats (13). It is generally recognized that gentle touch can have comforting effects for many animals (12,58,74,121,151). For instance, touch can markedly reduce heart rate in stressed dogs (66) and reduce isolation-induced vocalizing in young chicks (17,151). Thus tactile contact appears to be a sensory component of social attachment which has been conserved throughout evolution.

Another important sensory domain for affiliative behavior in rats is olfaction. Odors serve to signal and guide available social choices. Odors are the primary means of recognition in adult rats (48). Young rat pups seek out and show preferences for odors that have been associated with the mother and the nest (65,110,124); will preferentially suckle on nipples coated with an odor that is associated with the mother (167); and will preferentially huddle in the presence of nest odors (5). Home nest odors reduce the rate of ultrasonic vocalizations in young rats (137), and attenuate the behavioral activation induced by social isolation (52,187).

Additionally, odors experienced during the preweaning period may facilitate sexual behavior of adult male rats (59), and pup odors may play an important role in the induction of maternal behavior in recently parturient female rats. Interestingly, pup odors also function to actively inhibit pup-directed behavior in adult rats that have not recently given birth (61–63). Thus olfactory information serves to trigger and direct the affiliative behavior of both infants and adults.

Finally it is likely that milk plays at least some role in the formation of attachments in mammalian infants. Milk transfer is one of the primary functions of the mammalian infant–mother relationship. Milk infusion has been shown to induce a dramatic behavioral activation in rat pups (71), which is followed by a period of reduced activity, analgesia and calmness (20,22). Milk transfer appears to play an important role in regulating sleep–wake cycles and arousal patterns (29), and has been shown to induce odor preferences in rat pups (28,199). Thus milk transfer is likely to contribute to the funneling of behavior toward the mother, and as a stimulus around which infant behavior is organized.

There is considerable evidence that the aforementioned neurochemical systems (endogenous opioids, oxytocin, and norepinephrine), are physiological components of these sensory domains in infant rats, and form a core part of the physiological regulation of mother-directed behavior of preweanling rats. We will argue that these same neurochemical systems also participate in the affiliative behavior of juvenile and adult mammals of a variety of species. We believe this evidence indicates that the attachment and affiliative behaviors displayed by rats and other mammalian infants may represent the emergence of adult affiliative brain systems, and the ontogeny of a core attachment/affiliative motivational system in the brain.

ENDOGENOUS OPIOIDS

The analysis of opioid contribution to social attachment was premised on the apparent similarities between opiate addiction and social dependence. Both display an initial attachment phase, a tolerance-development phase, and similar symptoms during withdrawal phases (150,151). Consequently, it was suggested that ancient pain mechanisms may have provided the neural substrates for the evolution of separation distress mechanisms, and that separation distress and pain shared many neural systems (138,142).

The brain opioid theory of social attachment has now received a great deal of empirical support. As will be detailed below, there are many lines of evidence indicating that (a) opioids result in powerful attenuation of the reaction to social separation; (b) opioids are released during bouts of social contact; (c) opioids are rewarding and can induce odor and place preferences; and (d) low basal levels of opioids induce motivation to seek out social contact. These findings have been reported in a number of mammalian and avian species, and tend to generalize across developmental stages in which varied social contexts make different behavioral demands.

Attenuation of the separation reaction

Reductions in isolation-induced vocalizations (DV) following administration of opioid agonists were first reported in dogs (150), guinea pigs (76), domestic chicks (151) and primates (91). Subsequently, morphine and other opioid agonists were also found to reduce the frequency of isolation-induced ultrasonic vocalizations (USV) in preweanling rat pups (43, 94, 213). These vocalization

modulating effects have been primarily linked to the μ receptors (42,43,154).

Although the behavioral specificity of the opioid effects in infant rats has been questioned (213), there is now general agreement that the quieting effects in the other species is behaviorally specific. In other words, in species other than rats, DVs are reduced at very low, non-sedative doses. In fact, modulation of social behaviors with opiates is seen at lower doses than any other behavioral effects. However, in young rats, doses which reduce USVs also tend to reduce general activity. Young rats differ from both older rats and other species because they are extremely sensitive to opioids during the first 2 weeks of life, probably because of a greater permeability of the blood–brain barrier (10). Thus in young rats, the specificity of the social effects following administration of opiate agonists remains unresolved.

Studies with antagonists which only act to inhibit the action of endogenously released opioids do point to behavioral specificity, however. Naloxone and naltrexone block the vocalization-reducing effects of opioid agonists and, given alone, often potentiate the effects of social isolation (151). However, the potentiated isolation effect is not uniformly observed in all species. In our experience dogs do not show a potentiated isolation response following administration of opioid antagonists (150), but other species do including certain primates (91), guinea pigs (76,77), and under certain conditions, domestic chicks (147,163). The potentiated isolation effect is also mixed in rat pups, with some reporting a potentiation (45,93) and others not (213). Apparently, there are critical aspects of testing procedure that may be affecting the outcome of the various studies. These remain to be identified, but may include species differences, cirumannual variables and the amount of extraneous stress animals are exposed to during the separation experience (138).

Opioids are released by social stimuli

Several studies have indicated that endogenous opioids are released in response to a variety of social stimuli; two of these (milk transfer and somatosensory contact) are of particular relevance to infants. In neonatal rat pups and near term fetuses milk infusion induces a stereotyped stretch response which is coupled with reduced sensitivity to aversive perioral cutaneous stimulation (194), and increased hot plate withdrawal latency (22). These responses to milk are blocked by pretreatment with opioid antagonists (22,194) indicating that the behavioral reaction to the receipt of milk involves release of endogenous opioids. Interestingly, although both involve opioid receptors, there is apparently a shift from κ to μ receptor mediation of the behavioral response to milk between the initial and subsequent encounters indicating a perinatal reorganization (33,193,194,195).

In addition to milk, there is a fair amount of evidence that physical contact results in opioid release in a number of different species. Carden and Hofer (44,45) reported that when rat pups were placed in physical contact with an anesthetized, nipple-obscured dam fewer USVs were emitted, indicating that physical contact attenuates the separation reaction. This effect was blocked by pretreatment with the opioid antagonist naltrexone indicating opioid mediation. In older animals, affiliative social behavior is also thought to involve somatosensory-induced opioid release. Rats, like virtually all mammalian species engage in rough and tumble play during the juvenile period. Somatosensory interactions have been shown to be a critical component of this behavior (191), and this behavior appears to be mediated by opioids. Subtractive autoradiography studies have demonstrated that rough and tumble play results in the release of endogenous opioids (149), and naloxone blockade of opioid receptors reduces levels of play in rats (162). These findings indicate that opioids are both released by and contribute to the expression of play.

Finally, studies from other species have also reported contact-induced opioid release. β-Endorphin levels are elevated in CSF following bouts of allogrooming in monkeys (101). In adult mice, social contact has analgesic effects, and this is at least partially the result of opioid release (53,54); and young domestic chicks display a dramatic behavioral quieting response when placed in a cupped hand, which includes loss of muscle tone, closing of the eyes, and virtual elimination of DVs (151). Hence, like the quieting effect reported for young rats (45), this presumably somatosensory phenomenon in chicks is greatly attenuated by treatment with opioid antagonists, indicating that it too is mediated by release of endogenous opioids (152).

There is some controversy surrounding the findings that tactile contact induces opioid release in rat pups, however. In direct contrast to reports of Carden and Hofer (45), Blass and colleagues (21) reported that naloxone did not reverse the USV-attenuating effects of the mother. Furthermore, although suckling was found to dramatically increase pain tolerance in infant rats, this analgesic effect was not altered by pharmacological blockade of the opioid receptors (23). Additionally, Winslow and Insel (213) demonstrated that central administration of the opioid antagonist β-flunaltrexamine had no effect on isolation-induced vocalizations in rat pups, and no changes in opioid release were detected in several brain regions following contact with the mother, as measured by competitive diprenorphine binding. Thus the contribution of somatosensory-induced opioid release to rat pup affiliative behavior remains uncertain.

Rewarding effects

In addition to the powerful antinociceptive and isolation distress-alleviating properties of opioids, there is a great deal of evidence that endogenous opioids induce a euphoric state in animals. It has been postulated that, besides analgesia, one of the primary functions of endogenous opioids is to signal reward (16). Indeed the consummatory phase of several motivated behaviors appears to be signaled in part by release of endogenous opioids (1,19). This presumed euphoric property of the endogenous opioids is likely to be the primary reason animals will work for opioid infusions, and self administer opioid agonists. The positive affect induced by opioids not only functions to encourage animals to engage in consummatory behaviors, but also functions as an important reward substrate to induce learning. Stimuli which are present in the environment either just before or during opioid activation can result in both conditioned preference (47) and in conditioned activation of the opioid system (189). Thus stimuli which have been shown to induce opioid activation, such as milk transfer or possibly tactile contact, are likely to result not only in alleviation of

isolation distress, but also to produce a euphoric state, and induce subsequent preferences for the entire complex of social stimuli which are associated with this opioid activation (94). Indeed, in studies of social-attachment in young rat pups, it has been found that approach behaviors are diminished toward odors associated with maternal reunion in animals that had been treated with naltrexone prior to odor–mother pairing (158).

Opioid tone and social motivation

There are several studies which indicate that low basal levels of endogenous opioids may result in high levels of motivation to seek out social contact. Martel et al. (116) reported that naltrexone increased the frequency of social solicitations that young rhesus monkeys directed at their mothers, a finding which the authors attributed to a heightened drive for endogenous opioid release in the naltrexone-treated monkeys. This finding is also consistent with the observation that administration of opioid antagonists increased and opioid agonists decreased the motivation to receive social grooming in monkeys (101). Similar results have been found in guinea pigs and in adult rats, in which morphine was found to disrupt social cohesiveness, and reduce the tendency to seek out social contact (76,157).

Finally, Bridges (31) has suggested that opioid release may act to terminate bouts of suckling in maternal rats. Although this would be consistent with the opioid reward theory, these same authors have found that maternal rats display aversions to stimuli that were associated with opioid activation (102), suggesting that opioid release is aversive rather than rewarding in maternal rats. In this context it may be important to emphasize that acute injections of opiates have well-known aversive effects (188,210), some of which are peripherally mediated (15), that can lead to robust conditioned taste aversions. It is possible that the complex affective state induced by peripheral opiate administration complicates the interpretations of such findings.

Thus the brain opioid theory of social attachment posits that social isolation results in reduced levels of basal opioid levels and that social stimuli elicit release of endogenous opioids. This socially induced opioid release reduces the pain associated with social isolation, induces a euphoric state, funnels subsequent interactions toward social stimuli, and in essence may produce a social addiction. There is little doubt that opioids reduce the experience of pain, and induce a euphoric state. In addition there is evidence that pharmacological manipulation of opioids can reduce the emotional pain associated with social isolation (151) and some evidence that social interaction with the mother can induce release of opioids (22,45). Although the evidence is conflicting in some places, we believe these studies suggest that endogenous opioids are released by social stimuli encountered by infants prior to weaning. These same stimuli have been shown previously to induce behavioral preferences (5,28), indicating that opioids may participate in the formation of these preferences. Furthermore, similar findings from a number of different animals indicate that an opioid basis of social attachment may be a phenomenon which generalizes across a variety of social contexts (116). However both the generality and the theory itself remain controversial and there have been several negative findings reported (23,102,213).

We believe that the sheer number of studies reporting a role for endogenous opioids in social behavior is a testament to the brain opioid theory, but the negative reports are problematic, and suggest to us that refinements in the methodological approach are needed. For example, the discrepancies may largely be the result of the ambiguities that are inherent in the multiplicity of the opioid 'systems'. Several different peptides and receptor populations are affected by systemic administration of traditional agonists and antagonists (115), and endogenous opioids are involved in a large number of physiological processes (134). Therefore, systemic pharmacological approaches will certainly affect the functioning of many regulated systems that are unrelated to each other, and many unrelated stimuli will affect the release of endogenous opioids. Furthermore, opioid receptors are up-regulated in response to blockade (11,12), and apparently fluctuate in response to endogenous peptide levels (197). All of these problems make for noisy and inconsistent data. We believe that refinements in the definition and application of stimuli and greater precision in measurement will result in a clearer understanding of the role that opioids play in the regulation of social behavior.

It is also noteworthy, that work along these lines has already led to therapeutic interventions in humans, such as the use of naltrexone in the treatment of certain autistic children (135,140). But just as with the effects of opiate antagonists on DVs, the results in treating autistic children have also been mixed. In the positive studies, the most substantial effects of opiate–antagonist interventions appears to be on activity levels and attention, with more modest effects on social processes (41,155). There have also been several recent failures to find any robust therapeutic effects (39,40). Although naltrexone can benefit some children, (75,109,155,179) a clear therapeutic effect is only evident in a small subset of children, perhaps those that do, in fact, have excess brain opioid activity (26). Clearly, autism, like social bonding itself, is a multifaceted phenomenon that is not the result of actions within a single neuroanatomical or neurochemical system (14,68,180).

OXYTOCIN AND VASOPRESSIN

Evidence that the posterior pituitary peptide oxytocin plays a pivotal role in three behaviors of human females in which bonding often occurs (birth, breast-feeding and sexual behavior) initially led to the suggestion that oxytocin may regulate aspects of social bonding (103,128). A vast number of anatomical, comparative, and pharmacological studies conducted over the past 20 years have supported and extended this idea (e.g. (83)). However focus has shifted primarily to the central neuronal oxytocin projections rather than its peripheral or hormonal effects. As with opioids there is now evidence indicating that: (a) oxytocin attenuates the reaction to social separation; (b) oxytocin is released by social stimuli; (c) oxytocin participates in the formation of social preferences; and (d) oxytocin modulates affiliative behavior across a wide range of social contexts. In addition there is some evidence that vasopressin which is anatomically, evolutionarily, and functionally related to oxytocin may also participate in social affiliation.

Oxytocin attenuates the separation reaction

In a series of comparative studies, Shapiro and Insel

(87,186) focused on the neuroanatomy and behavior of two closely related species of vole that have vastly different adult social structures. A higher density of oxytocin binding sites was found in several regions of the central nervous system of the social living species than in the solitary living species (87). Furthermore, a heightened behavioral reaction to social isolation was found in the social living infant (186) indicating that not only is the adult social structure reflected in the affective patterns of infants, but also that oxytocin may underlie social interactions during both periods.

In addition to these findings, central administration of oxytocin has been found to reduce the frequency of isolation-induced USV in young rat pups (88). These findings further suggest a possible role for central oxytocin release in the affective 'calm' response infants display during social contact. Furthermore, central administration of an oxytocin antagonist has been found to block the acquisition of a maternally associated odor preference in young rat pups (127). This finding suggests that endogenous release of oxytocin is necessary for the formation of maternal–odor associations in preweanling rats. Finally, reductions in oxytocin receptor binding have been reported in the hippocampus of the neonatal rat after undergoing brief periods of social isolation (131). Although the behavioral implications of this finding are not clear, they do indicate that oxytocin release is likely to play an important role in social interaction with the mother, and that oxytocin is tightly regulated in young rats.

Interestingly, in addition to rodents, the isolation reaction of young chickens is also greatly attenuated by oxytocin administration (139,142,143), in spite of the fact that avian species do not produce oxytocin endogenously. However, since the ancestral molecule vasotocin produces the same result at essentially the same doses (143), we can surmise that the comforting effect of oxytocin is the result of oxytocin's actions on the pre-existing vasotocin systems of ancestral species.

Social stimuli may induce oxytocin release

There is clear evidence that oxytocin is released from the posterior pituitary of female mammals during vaginal stimulation (100) nursing (207), and parturition (64), all of which occur during social interactions. This hormonal release may well be accompanied by generalized activation of oxytocinergic cells within the paraventricular nucleus of the hypothalamus and thus reflect central oxytocin release as well. There is, however, much less evidence for the stimuli which may elicit oxytocin release in infants or males, or in females in non-reproductive social settings.

It is plausible, that like opioids, oxytocinergic neurons are activated by generalized physical contact. Recent studies have found that oxytocin levels increase in both blood and cerebrospinal fluid of rats after receiving gentle vibrotactile or thermal stimulation (203). Finally, Blass et al. (21) recently reported that physical contact with an anesthetized dam induced an opioid-independent analgesic response in young rat pups, and a similar observation has been made by Panksepp (unpublished data, 1980). An opioid-independent analgesic property has been attributed to oxytocin, leading to an easily testable possibility that this analgesic response may be mediated by endogenous oxytocin release.

There is also a fair amount of evidence that oxytocin participates in ingestive behavior. Oxytocin is released in response to systemic administration of CCK, and gastric distention, and reduces food and fluid intake in adult rats (9,118,133,206). Recently oxytocin has also been found to reduce milk intake in infant rats (123). These results indicate that oxytocin may act as a satiety agent in both adult and infant rats, and suggest that in addition to physical contact, milk transfer may act to release oxytocin in mammalian infants.

Oxytocin increases affiliative behavior and induces social preferences

There is a great deal of evidence suggesting that oxytocin participates in affiliative behaviors, not only during the preweanling period, but also at several other times throughout the life of several mammalian species, including the rat. Oxytocin receptors proliferate in many forebrain areas including the medial preoptic area, ventromedial hypothalamus, and bed nucleus of the stria terminalis of female rats at the time of parturition (82,89,165). This proliferation is apparently triggered by high circulating levels of estrogen (89). Changes in oxytocin receptors may be related to the induction of maternal behavior since intraventricular and preoptic area infusion of oxytocin induces a rapid onset of maternal behavior in virgin female rats (165,166). Furthermore, maternal behavior is greatly impaired in post-parturient rats that received paraventricular nucleus lesions during pregnancy (85), and in female rats administered oxytocin antiserum soon after parturition (205). Thus, central oxytocinergic activity may be functionally related to the initiation of maternal behavior after birth.

Oxytocin has also been found to play a role in reproductive behavior. Central infusion of oxytocin induces penile erections in male rats while PVN lesions and central administration of an oxytocin antagonist inhibit erections (8). Both central and peripheral oxytocin administration have been found to facilitate lordosis in hormone-primed female rats (69), and central administration of an oxytocin antagonist was found to reduce sexual receptivity in female rats (217). These findings point to a possible role for both peripheral and central oxytocin in the appetitive phase of sexual behavior in male and female rats. In addition, a large surge of oxytocin has been reported in the blood of several mammals including humans of both sexes at sexual climax (46,49), suggesting a possible role for oxytocin in the consummatory phase of copulatory behavior as well.

There is evidence that oxytocin may modulate group aggregation behavior in some species, as well. Insel and Shapiro (87) reported that oxytocin receptor numbers differed dramatically in two closely related species of vole, with the group living and gregarious Prairie vole having more oxytocin receptors in most brain regions than the solitary living Montane vole. Additionally it has been found that chronic central infusion of oxytocin to male rats in the presence of specific females increases non-sexual social interaction directed toward those females (218). Oxytocin has been shown to increase social interactions in a number of species. Both prairie voles and rats display enhanced physical contact following central infusion of oxytocin (216,218) and, under some circumstances, oxytocin increases the allo-grooming activities of male squirrel monkeys (214).

Furthermore, there is some evidence that specific preferences may develop to social stimuli experienced in the presence of oxytocin. Female prairie voles exposed to a male just after receiving a central oxytocin infusion subsequently displayed a preference for that male over other males, and exposure to a male in the presence of central oxytocin blockade prevented acquisition of that preference (211). Additionally, oxytocin has been implicated in the selective preference that ewes display for the odors of their lamb over other 'strange' lambs to which they have not given birth (98,99).

Oxytocin has also been found to facilitate social memory. Infusion of oxytocin into the medial preoptic area following a social encounter prolongs the decline in investigatory behavior that ordinarily occurs in subsequent encounters with the same animal (171), a finding which the authors attributed to potentiated social memory consolidation, although other behavioral effects, or even less accurate memory could produce similar results. Oxytocin has also been found to potentiate a socially induced gustatory preference in rats (170). However, these pharmacologically induced mnemonic effects of oxytocin only occur at relatively low doses. Higher doses have typically been found to have amnestic effects (56).

Oxytocin also appears to play a role in the olfactory-based memory that maternal sheep form of their offspring during the 2–4-h 'bonding window' after parturition. These studies have revealed that there is an increase in oxytocin concentration in microdialysis samples from the olfactory bulb of recently parturient sheep following presentation of odors from their offspring, but not following presentation of strange lamb odors (95). This evidence in conjunction with findings that central infusion of oxytocin participates in maternal acceptance behaviors in post parturient sheep (99), and that vaginocervical stimulation, such as would occur during birth results in oxytocin release (100), have led to the speculation that oxytocin release plays an important role in postpartum memory formation in sheep.

Oxytocin knockout mice

Recently a mutant line of mice was created in which the DNA coding sequence for oxytocin was deleted (129). These 'oxytocin knockout mice' fail to produce endogenous oxytocin in detectable levels, yet they show very few ill effects of this treatment. Contrary to what would have been predicted from the lesion and pharmacological literature (conducted primarily on rats), both male and female knockout mice display normal mating behavior, and produce live offspring. Female mutant mice undergo normal pregnancy, do not appear to have any difficulties with parturition, and generally display normal maternal behavior. The only striking abnormality in the knockout mice was an apparent inability to induce milk ejections. If left with the mutant mother, knockout infants starved to death because they could not extract milk from their mother. However if milk ejections were induced in maternal mutants via exogenous oxytocin administration, pups survived through weaning (129). Although preliminary reports indicate that some social abnormalities might be present in these mice when closer scrutiny is applied (219), the general lack of impairment in these mice is striking. Perhaps the most surprising finding of all was that oxytocin was not required for labor. This finding challenges the understanding of the mechanisms which underlie labor that have been held for over 40 years. The authors have suggested that labor may have been induced in these mice by some unknown substance acting on the oxytocin receptors which were not affected by the gene deletion (129). Similar compensatory mechanisms may be occurring throughout the brain and explain the null effects on maternal and sexual behavior. Clearly this technology will hone our understanding of oxytocin's role in reproduction and social behavior, however at this point it is difficult to interpret the data generated from these mice.

Vasopressin

Although not as extensive as the oxytocin literature, a similar affiliative role has also been suggested for the closely related nonapeptide vasopressin. Vasopressin reduces USV frequency in isolated young rat pups (215), and an attenuated maternally associated odor preference has been found in the vasopressin-deficient Brattleboro strain of rat ((125), and see below). These findings suggest that vasopressin, like oxytocin may be involved in emergent affiliative processes in young rats.

Vasopressin has also been implicated in the onset of maternal behavior, although its effects are neither as strong nor as rapid as oxytocin (164). Vasopressin has been linked to paternal behavior in the Prairie vole. Testosterone-dependent increases in vasopressin immunoreactivity occur in forebrain areas of the male Prairie vole soon after mating (209), and central infusions of vasopressin increase

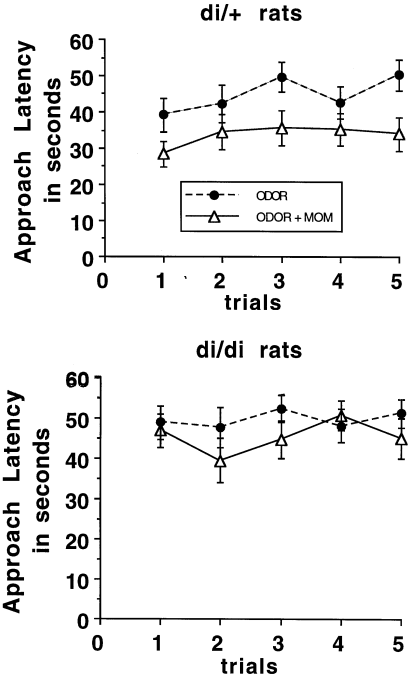

FIG. 2. The latency for vasopressin-producing di/ + (top panel) and vasopressin-deficient di/di (bottom panel) 15-day-old rats to approach an odor contained on a cotton ball at the end of a 35-cm long runway across five testing trials. On the previous day the pups had been exposed to the odor on the ventral surface of the mother or on a cotton ball. The vasopressin producing di/ + rats approached the odor significantly faster if paired with the mother than with a cotton ball ($P < 0.05$). However no difference existed for the vasopressin-deficient di/di rats.

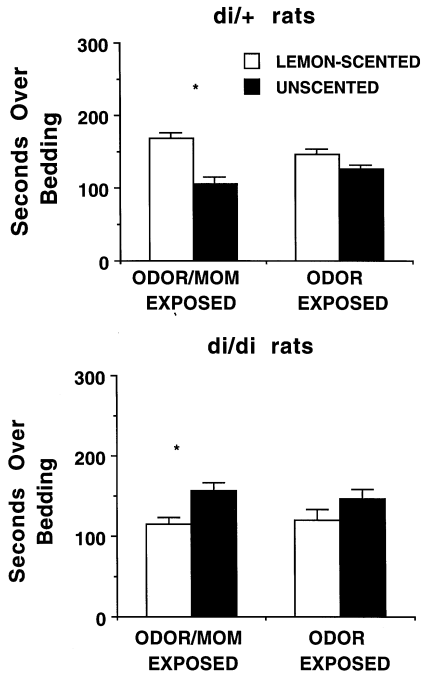

FIG. 3. The duration spent over bedding scented with the paired odor versus the duration spent over unscented bedding for vasopressin-producing di/ + (top panel) and vasopressin-deficient di/di rats (bottom panel). Significantly more time was spent over scented than unscented bedding in odor–mother paired di/ + rats ($P < 0.05$). However odor-mother paired di/di rats displayed a significant aversion to the scented bedding ($P < 0.05$).

the incidence of paternal behaviors, while central infusions of antagonists reduce the incidence of these behaviors (208).

Although no direct role for vasopressin has been found in sexual behavior (e.g. erections, lordosis), administration of a vasopressin antagonist after copulation prevented the formation of post-copulatory pair bonds in the male Prairie vole and, in the absence of copulation, vasopressin administration was found to induce pair-bond formation in this species (212). Thus, vasopressin may play an important role in post-copulatory sexually induced attachment in the males of some species. These findings indicate that oxytocin and vasopressin may work in conjunction with gonadal steroids to induce gender-specific social behavior.

Several studies have demonstrated a role for vasopressin in social memory. Both intraventricular and intra-septal infusion of vasopressin have been shown to prolong the period of suppressed exploratory activity that occurs following exposure to social stimuli (55) and vasopressin agonists, like oxytocin, have also been found to potentiate a socially induced gustatory preference in rats (170).

Finally, as has been alluded to previously, we have recently employed an experimental model of attachment in infant rats in which a novel odor is repeatedly paired with the mother. After three such pairings, Long-Evans rats display both a preference and a decreased approach latency for this odor (see (127) for experimental details). However rats of the Brattleboro strain which do not produce endogenous vasopressin (Db/Db) fail to develop either odor preference or reduced approach latency following similar training (Figs. 2 and 3). Although vasopressin-deficient rats are likely to differ on many dimensions, these results are consistent with a role for vasopressin in social attachment possibly by modulating social memory (67,56).

Thus there is a large body of literature from several different species which indicates that the neurohypophyseal peptides are involved in the neurophysiology of a variety of different affiliative behaviors. It is also worth noting that oxytocin, especially through its proline–leucine–glycine tail, can inhibit opioid tolerance (104), and that the opioid antagonist naloxone is a potent inducer of peripheral oxytocin release in rats (18,60), suggesting the possibility that these two social reward systems may interact in important ways.

NOREPINEPHRINE

In addition to the affective and motivational components that have been linked to neuropeptides, learning and memory plays an important role in social attachments. Learning gives specific direction to pre-wired behavioral patterns. For example, infant rats will suckle, huddle, and seek out the mother, but all of these behaviors have been shown to be amenable to directing and funneling with environmental cues. The primary environmental cue used in social learning by rats is olfaction. Odors are particularly important stimuli for the neonatal rat pup which is born deaf and blind (190), and odors continue to be an important guide for social behavior throughout the life span of the rat. Odors affect behavior of young rats through genetically preprogrammed responses such as innate preferences for soiled bedding (65). However, a great deal of both associative and non-associative odor learning also occurs in rat pups (65), and hence novel odors can also act as important behavioral guides for the preweanling rat (167,177,199).

Several recent studies have pointed to both oxytocin and vasopressin as important modulators of social memory. We have attempted to touch on this literature here, but this has been extensively reviewed recently (56). In addition to a role for these peptides, norepinephrine (NE) appears to play an important role, particularly in the neurophysiological component of olfactory learning in both neonatal and adult rats. Sullivan and colleagues have demonstrated that neonatal rats will display a preference for an odor that has previously been associated with stroking the dorsal surface with a paintbrush (199). This behavioral learning is accompanied by an odor-specific morphological change in the olfactory bulb (200). In other words, rats which had been exposed to brush–odor pairing displayed both an odor-specific behavioral preference and displayed differences in odor processing at the level of the olfactory bulb relative to rats which received the odor alone, the brushing alone, or the odor and brushing in a random non-associative manner (199,200). Furthermore, both the behavioral preference and the physiological responses to the stroke-associated odor were blocked in rats that received the NE antagonist propranolol prior to odor–stroke pairing (201). Although, propranolol did not block the expression of a previously acquired odor preference, indicating that NE release is important in the formation of the odor memory, but not for the detection of the odor or the execution of behavioral preferences once memories were formed. Furthermore pairing of the NE agonist isopreterenol with an odor in lieu of stroking also induced both the behavioral preference and the olfactory bulb changes, indicating that induction of NE activity is sufficient for both of these processes to occur. Presumably, NE release participates in the induction of the

morphological changes in the olfactory bulb, and the production of the odor engram, by altering odor processing within the olfactory network. But once this engram is formed, NE is not necessary for expression of the olfactory memory or for brain engram maintenance (201).

Very similar findings of a role for odor learning and NE in the olfactory bulb have been reported for maternal rats as well. While the rapid initiation of maternal behavior appears to be largely influenced by postpartum hormonal and neurochemical influences, the long-term maintenance of maternal behaviors (i.e. 10–18 days after parturition) appears to be largely a function of experience with pups. Post-partum hormonal levels decline to prepartum levels 7 days after birth, as does the maternal behavior of post-parturient rats that are not allowed any contact with pups. However post-partum rats that are allowed a short period (30 min) of interaction with pups after birth, will continue to have heightened levels of maternal responsiveness long after birth (135). A short period of interaction with pups appears to be necessary for the continued long-term maintenance of maternal behaviors in post-partum rats (135). Thus there are both physiological and experiential determinants of maternal behavior in the rat. This maternal experience effect appears to be largely (although not exclusively) olfactory based. Postpartum exposure to distal pup stimuli is sufficient to significantly potentiate maternal behavior 10 days later, although this effect was not as strong as full exposure to pups (135). The continuation of maternal behavior also appears to rely on NE, as post-partum exposure to rat pups that was followed by NE receptor blockade was less effective in promoting long-term maternal behavior than exposure to pups followed by saline administration. On the other hand, administration of a NE agonist following exposure to pups potentiated the post-partum pup exposure effect (120).

In a similar vein, parturition stimulates maternal behavior in mice, but it will not prevent maternal mice from engaging in cannibalism. Exposure to distal pup stimuli (auditory and olfactory) after birth is necessary for the inhibition of cannibalism, presumably because maternal mice have formed an olfactory-based memory of their offspring (36). Depletion of NE content in the olfactory bulb prevented the inhibition of cannibalism after either full or partial prior exposure to pups (36). And exposure to pups was found to induce NE-dependent neural activity in olfactory bulb and pyriform cortex of female mice (35).

The Bruce effect (i.e., olfaction-induced pregnancy block) is another odor learning phenomenon in female mice that appears to be NE dependent. If female mice are exposed to the urine of a male other than the one they mated with during a short period after pregnancy, they will abort the fetus. These abortions are dependent upon the formation of a specific memory for the mated males' urine, and this memory appears to be NE dependent (176).

Olfactory recognition of offspring has also been found to play an important role in the maternal behavior of sheep. Ewes have a 2–4-h period after birth in which they form a selective 'bond' with their offspring. Approaches and solicitations from lambs that the ewe did not come into contact with during this critical bonding window will generally be repelled (169), even if it is her own offspring. As with rats and mice, this maternal memory phenomenon in sheep appears to be both olfactory based and NE dependent. Kendrick et al. (96,98) report that parturition induces a considerable amount of reorganization in the olfactory bulb of sheep, with a number of mitral cells altering their response characteristics to preferentially respond to lamb odors. This may be partially the result of NE projections, as spikes of NE have been found in the microdialysates of the olfactory bulb of sheep coincident with parturition and uterine contractions (113), and after exposure to lamb odors during the bonding window, but not prior to parturition (98). A direct role for NE in maternal learning is implicated by the finding that infusion of propranolol into the bloodstream of sheep during the post-partum bonding window significantly reduced the number of sheep that discriminated between their own and alien lambs (112).

In addition to the hormonal changes which occur during pregnancy, vaginal stimulation which occurs during the birthing process may play an important role in inducing some of the alterations in olfactory bulb physiology which make this rapid bonding possible. Providing vaginocervical stimulation to ewes after the 'bonding window' closes is sufficient to induce maternal behavior (100) and to re-open the bonding window (97). Interestingly, vaginocervical stimulation (VCS) has been found to result in a variety of physiological responses in the central nervous system, including release of oxytocin (99).

Thus, it is possible that VCS is a basic mammalian mechanism for the induction of odor memories during biologically relevant periods. Furthermore, the VCS-induced oxytocin release is potentiated by pretreatment with morphine (99), and recently oxytocin has been shown to induce NE release both in the olfactory bulb (114) and in the medial preoptic area (96) of sheep, suggesting that NE release may represent a final pathway for oxytocin effects in ewes.

Thus there are several examples from early affiliative behavior to maternal behavior to reproductive behavior indicating that NE projections to the olfactory bulb play a key role in the formation of olfactory-based social memories. We believe this to be an important final pathway in the social bonding and formation of social memories of many mammalian species. It should be emphasized that the role of NE in this process is likely to be one of an enabler of engram formation, rather than the execution of social behaviors or even a means of storing the olfactory engram itself. Norepinephrine projections to the olfactory bulb are thought to disinhibit mitral cell activity by reducing GABA activity (30,36,98). This disinhibition results in amplification of the olfactory signal, which in turn induces long-term changes in the olfactory neural network not unlike those attributed to long-term potentiation (30,36,98). Thus the role of NE in the social bonding systems described above is to work in conjunction with limbic circuits to create plasticity within the olfactory bulb enabling meaningful olfactory signals to form a lasting imprint (34,98).

Finally, a neurobiological theory of primate attachment has recently been put forth which argues for a pivotal role for cortical NE (105). A detailed description of this theory is beyond the scope of the present review, however it should be noted that this theory puts forth a critical role for NE release within the neocortex for the organization of social affect in primates, and suggests that this NE release is associated with social learning. It has been shown that primates that have experienced any form of maternal isolation, including rearing with peers, which prevents many of

the behavioral deficits of socially isolated animals, exhibit reduced brain NE metabolism (105). Thus although the neural organization might be quite different, one can imagine that slight changes during the course of evolution may have resulted in altering 'social attachment circuitry' from one involving NE-based changes in the olfactory bulb, to one involving NE-based changes in the neocortex.

OTHER NEUROCHEMICAL SYSTEMS WHICH MAY MODULATE THE AFFILIATIVE CIRCUIT

Thus, there is strong evidence that oxytocin, endogenous opioids, and NE play important roles in affiliative behaviors that emerge in young rats, and that these neurochemical systems continue to play an important role in affiliative behaviors in adult rats as well as other mammalian species. We would suggest that these neurochemical projections work together as a part of a unitary brain process or affiliative circuit which regulates mammalian affiliative behavior (Fig. 1). In this view, attachment behaviors displayed by infants represent the emergence of this system. There are almost certainly other components which contribute to this system.

There is some evidence that the endogenous benzodiazepine receptor complex may participate in the regulation of social interaction in young rats. The benzodiazepine antagonists, diazepam (86) and chlordiazepoxide (45), have been found to reduce isolation-induced vocalizations in rat pups and the benzodiazepine receptor agonist pentylenetetrazol has been found to increase the rate of ultrasonic vocalizing (86). Furthermore, social isolation has been found to reduce the number of available binding sites for an exogenous benzodiazepine antagonist in several brain areas suggesting that social isolation results in the release of a benzodiazepine agonist (84) Additionally, Carden and Hofer (45) found that the benzodiazepine receptor antagonist RO 15-1788 blocked the locomotor-reducing effect of the dam in young rats, indicating that the dam-associated activity reductions may involve the release of an endogenous benzodiazepine agonist. However this same agent did not reverse the dam-induced reductions in USV (45), suggesting that although an endogenous benzodiazepine agonist may be released in the presence of the dam, this molecule does not appear to be necessary for the reductions in USV. Further evidence of a role for this system comes from the finding that GABA spikes appear in the microdialysis samples from post-parturient sheep following presentation of lamb odors (96), and GABA binds to the benzodiazepine receptor complex.

Although the benzodiazepine receptor complex probably is playing some role in the modulation of affiliative behavior, it is such a widespread 'system' that it is difficult to include in a proposed general circuit at the present time, especially since the above pharmacological effects are not very robust in other social species ranging from young domestic chicks (156) to dogs (182) to primates (92). Pharmacological activation of this receptor system probably changes the general activational state of the organism, which certainly fluctuates with, but is not specific to social separation. Thus non-specific effects remain a possible source of the above effects. Also, it must be remembered that fear systems do exist in the brain which are distinct from those which mediate separation distress (141), and it is possible that the aforementioned experiments in infant rats entailed substantial arousal of that system. Still, the findings by Insel et al. (84) that an endogenous molecule (DBI) is apparently released during social isolation which binds to the benzodiazepine receptor complex is compelling and warrants further study, but the lack of generality and specificity at present makes it difficult to include endogenous agents of the benzodiazepine receptor complex such as GABA or DBI as either a major or a critical component of the affiliative circuit.

Another neurochemical which may modulate social comfort and isolation is prolactin. Prolactin has recently been found to dramatically reduce isolation-induced vocalizations (145), and some of the maternal behavior facilitation that can be produced by estrogen treatment may be mediated in part by prolactin (31,122,169). There is also some evidence for the inclusion of melatonin (126), and serotonin (119,90,136,156,172) in the neurobiology of affiliation. Serotonin is especially promising since a great deal of human data, most of it anecdotal (106), suggest that facilitation of serotonin promotes social confidence and a feeling of connectedness to others. Also a reduction of brain serotonin activity is one of the clearest neurochemical effects of prolonged social-isolation (90,204), further suggesting a role in the regulation of social behavior. Obviously, a great deal more work is needed on these systems as well as many others that have been revealed by modern neuroscience.

Adult modifications of the affiliative circuit

If a common brain circuit does indeed underlie affiliative behavior from birth through death, it is clear that the affiliative circuit undergoes changes over the course of development. The expression of oxytocin receptors for example has been shown to be highly dynamic from birth through puberty in rats (185,202). Dramatic changes are associated with weaning, puberty and parturition and these periods also involve dramatic reorganization of social behavior.

There are changes in the neurophysiological control of ingestion which occur with weaning (71) and these may be reflected in alterations of associated social circuitry. Additionally gonadal steroids appear to exert strong regulatory influence on opioids, oxytocin and vasopressin (32,37,38,89,168,209). For example, estrogen stimulates oxytocin receptor proliferation (89) and oxytocin synthesis, and receptor affinity (37,38). Estrogen may induce increases in endogenous opioid functioning as well (32,168). Conversely, testosterone selectively increases the functional capacity of vasopressinergic cells (209). Thus, the onset of puberty and large-scale increases in the synthesis and secretion of gonadal steroids, could exert widespread changes and shifts in emphasis throughout the proposed affiliative circuitry of the brain. This circuit would also undergo functional changes during other periods of time when gonadal steroids were elevated such as mating and pregnancy.

Clearly other factors emerge during the course of ontogeny, which may include both genetically programmed and environmentally acquired factors which are likely to affect the functioning of this circuit. Such environmentally acquired factors would certainly be needed to explain the findings that the preweaning social environment of some

mammals has long-term consequences on the sexual behavior of adults (51,59). Obviously an understanding of social attachments will have to include such acquired and programmed alterations of organic brain processes in any comprehensive explanation of how early social relationships exert long-lasting influences on affiliative behavior. Many studies now indicate that both early and late modifications of brain affiliative systems do occur, and it may be time to empirically reassess the role of critical or sensitive periods (183) in the manifestations of affiliative circuits within the brains and psychobiological dispositions of mammals.

Ultrasonic vocalizations, thermoregulation, and evolution

Of all the behaviors displayed by the isolated rat pup, USV has received the most attention by far. This is probably due largely to the fact that USVs are readily produced in rat pups, are easy to quantify, and resemble a similar behavior in separated human infants. However, although many authors have assumed that USVs represent the communication of distress produced by social isolation, it has been argued that USVs represent the acoustic byproduct of increased oxygen consumption because of energy demands of thermogenesis ((25), but see (80)), There is no doubt that USVs in rat pups and the sonic DVs in the other species discussed in this review are very sensitive to ambient temperature (6,184), and USV in the rat may represent a very early transitional point from physiological reaction to direct regulation of social behavior. If USVs are indeed merely an index of thermogenesis in rats, then this may represent a very interesting point in the phylogeny of affiliation (Fig. 1). Several of the neurophysiological controls of USV in rat pups have also been found to control other social behaviors in adult rats (49) and isolation-induced vocalizations in species other than rat (142), where ambient temperature clearly plays less of a role. Whether the neurophysiological controls of rat pup USVs are the result of altering the 'distress' or 'comfort' (80,160) systems of the brain or merely an indication of enhanced oxygen intake (25), USVs do result in obtaining the care and attention of the mother (7), and the thermoregulatory system which inadvertently functioned to elicit maternal care may have become elaborated over both phylogenetic and ontogenetic time to mediate non-thermal social behaviors as well. The ancient thermal message may have remained within the infrastructure of social affect (4). Thus what was initially a physiological system which served thermoregulatory functions may have been co-opted by social needs of the young animal, and used in a novel way. If this is the case, this would be a classic example of what Gould and Vrba have referred to as exaptation (24,70), which as we described at the outset is the principle evolutionary history of the proposed affiliative circuit.

The polyvagal theory of emotion recently postulated by Porges (173) may provide another potentially fruitful evolutionary framework from which to view the vocalization literature. Porges argues that refinements in the control of metabolism have emerged through evolution which have produced a hierarchically organized system of mobilizing resources in order to control metabolic output. The most recently evolved component of this system is tonic vagal inhibition of cardiac output. This component involves direct neural access to a tonic cardiac brake enabling rapid control over metabolic output by disengaging and engaging this system. The second and phylogenetically older means of resource mobilization is driven by activation of the sympathetic nervous system. Engagement of this system mobilizes resources from the entire organism via adrenal activation. Finally, phylogenetically the oldest means of adaptation involves reducing rates of respiration and heartrate to conserve resources.

According to the polyvagal theory, this system is engaged hierarchically in reverse phylogenetic order. In other words in response to challenges, mammals will tend to initially modulate cardiac inhibition, and then engage the sympathetic nervous system before they would resort to extreme metabolic conservation (173). This hierarchical system seems to be quite applicable to the expression of USVs in rat pups. Under nest temperatures, USV levels in rat pups have been shown to be modulated by intra-oral milk infusion which is likely to engage the tonic inhibition of metabolic activity through vagal engagement (22). Slightly stronger metabolic challenges are likely to be produced by extreme cold which results in enhanced oxygen consumption and utilization combined with pronounced increases in USV rate (25). Finally, prolonged periods of separation from the mother or extended thermal challenge results in reductions in both basal metabolic rate and USV frequency (78,79).

SUMMARY AND CONCLUSIONS

Although different in important ways, the preweanling rat does express some of the fundamental affiliative behavior patterns that are found in humans and other mammals. This can be both an advantage and a disadvantage. One advantage is that commonalities which emerge between the physiology of rat and other species' affiliative behavior may represent an important core of mammalian affiliative physiology upon which all other complexities are based. One important disadvantage is that a study of certain response patterns, such as separation-induced vocalizations, may be harder to generalize to the social affiliative behavior of other species. Approach and behavioral choice measures may be more informative measures of attachment, especially in the rat.

Obviously, a great deal remains to be learned about the neurophysiological mechanisms of affiliative behaviors in all species including preweanling rats, however some important findings as well as new conceptual paradigms have emerged in recent years. These have led us to the theory that basic, genetically promoted, species-typical affiliative patterns are reflected in specific brainstem and limbic circuits of the mammalian brain (for a complete summary, see (146)). In infant rats and many other species, these affiliative patterns are largely thermo-tactile and possibly gustatory and they are probably all modified specifically by oxytocin, vasopressin, and endogenous opioid peptides. Environmental stimuli particularly odors can modify and direct these behaviors through associative, non-associative and other means (see (2)). NE within the olfactory bulb is largely responsible for olfactory learning and olfactory bulb plasticity, which appears to participate in the funneling of affiliative behaviors toward specific social targets.

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